

The 35 U.S.C. § 112, second paragraph, rejection

The Examiner rejected claims 17 and 20 under 35 U.S.C. § 112, second paragraph, as indefinite for reciting the term "indication". This rejection is respectfully traversed.

It is Applicant's position that the metes and bounds of the phrase "indication" in the context of the claims is clear. Evidence to that effect is found at page 865 in Stedman's Medical Dictionary (Williams & Wilkins (1995), a copy of which is provided herewith), where indication is defined as the "basis for initiation of a treatment for a disease or of a diagnostic test, may be furnished by a knowledge of the cause..., by the symptoms present or by the nature of the disease."

Even if, assuming for the sake of argument, the metes and bounds of the phrase "indication" were not readily recognizable to the art worker, exemplary indications falling within the scope of the claims are provided in Applicant's specification. Applicant discloses that indications associated with chemokine-induced activity, such as aberrant or pathological inflammatory processes (page 18, lines 9-10 and page 98, lines 9-10) include: atherosclerosis and other forms of local or systemic vasculitis, diseases such as myocardial infarction, stroke and acute ischemia which are secondary to atherosclerosis; hypertension; reperfusion injury; aortic aneurysms; vein graft hyperplasia; angiogenesis; hypercholesterolemia; congestive heart failure; Kawasaki's disease; stenosis or restenosis, particularly in patients undergoing angioplasty; pathologically low bone mineral density, such as osteoporosis; ulcerative colitis; chronic obstructive pulmonary disease; infection with HIV, other lentiviruses or retroviruses with similar mechanisms of cell entry via chemokine receptor(s), or infection with other viruses, e.g., cytomegalovirus, or viral infection resulting in viral meningitis; organ transplantation, such as acute transplant rejection, allograft rejection and graft versus host disease; transplant vasculopathy; malaria and other consequences of infection by parasites related to plasmodium; asthma; allergic diseases, such as atopy (IgE-mediated components), allergic rhinitis, atopic dermatitis, anaphylaxis, allergic bronchopulmonary aspergillosis (IgE-mediated), and hypersensitivity pneumonitis (high IgG and reactive T cells) (pigeon breeders disease, farmer's lung disease, humidifier lung disease, malt workers' lung disease); allergies, including flea allergy dermatitis in mammals such as domestic animals, e.g., dogs and cats, contact allergens including mosquito bites or other insect sting allergies, poison ivy, poison oak, poison sumac, or

other skin allergens; urticaria; eczema; pulmonary fibrosis such as idiopathic pulmonary fibrosis; cystic fibrosis; hemolytic uremic syndrome; autoimmune disorders, including, but not limited to, type I diabetes, Crohn's disease, multiple sclerosis, arthritis, rheumatoid arthritis, systemic lupus erythematosus, autoimmune (Hasimoto's) thyroiditis, autoimmune liver diseases such as hepatitis and primary biliary cirrhosis, hyperthyroidism (Graves' disease; thyrotoxicosis), insulin-resistant diabetes, autoimmune adrenal insufficiency (Addison's disease), autoimmune oophoritis, autoimmune orchitis, autoimmune hemolytic anemia, paroxysmal cold hemoglobinuria, Behcet's disease, autoimmune thrombocytopenia, autoimmune neutropenia, pernicious anemia, pure red cell anemia, autoimmune coagulopathies, myasthenia gravis, autoimmune polyneuritis, experimental allergic encephalomyelitis, pemphigus and other bullous diseases, rheumatic carditis, Goodpasture's syndrome, postcardiotomy syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, and scleroderma; eye diseases such as uveitis or blinding Herpes stromal keratitis; liver disease; erlichiosis or Lyme disease including Lyme arthritis; aberrant hematopoiesis; nephritis due to, for example, autosomal dominant polycystic kidney disease, diabetic nephropathy, IgA nephropathy, interstitial fibrosis, or lupus; as well as other disease states resulting from inappropriate inflammation, either local or systemic, for example, irritable or inflammatory bowel syndrome, psoriasis, delayed type hypersensitivity, Alzheimer's disease, chronic pulmonary inflammation, e.g., pulmonary alveolitis and pulmonary granuloma, gingival inflammation or other periodontal disease, and osseous inflammation associated with lesions of endodontic origin, hypersensitivity lung diseases such as hypersensitivity pneumonitis, and inflammation related to histamine release from basophils, such as hay fever, histamine release from mast cells, or mast cell tumors, types of type 1 hypersensitivity reactions (anaphylaxis, skin allergy, hives, allergic rhinitis, and allergic gastroenteritis); glomerulonephritis; inflammation associated with peritoneal dialysis; pancreatitis; neoplasia, e.g., histiocytoma, glioma, sarcoma, osteosarcoma, osteoma, melanoma, Kaposi's sarcoma, small cell lung cancer, and ovarian carcinoma as well as myelosuppression and mucositis associated with chemotherapy; brain or spinal cord trauma, such as after disc surgery; gout; lung disease, e.g., due to respiratory syncytial virus infection of humans, cattle, pigs and the like, or lung injury; strokes; Loeffler's syndrome; chronic eosinophilic pneumonia; pulmonary fibrosis; wound healing; bacterial infection, e.g., bacterial peritonitis or meningitis;

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granulomatous diseases such as Mycobacteriosis, Pneumocystosis, Histoplasmosis, Blastomycosis, Coccidiomycosis, Cryptococcosis, Aspergillosis, granulomatous enteritis, Candidiasis, foreign body granulomas and peritonitis, pulmonary granulomatosis, Wegener's granulomatosis, leprosy, syphilis, cat-scratch disease, schistosomiasis, silicosis, sarcoidosis and berylliosis; lethal endotoxemia; and indications associated with a weak inflammatory response, e.g., which occur in parasitic infection, e.g., *Leishmaniasis*, trypanosome, *Mycobacterium leprae* or *Mycobacterium tuberculosis* infection, helminth infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (fluxes) (Schistosomiasis, Clonorchiasis), cestode (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral works, visceral larva migrans (e.g., *Toxocara*), eosinophilic gastroenteritis (e.g., *Anisaki* spp., *Phocanema* spp.), cutaneous larva migrans (*Ancylostoma braziliense*, *Ancylostoma caninum*), or fungal infection; acute respiratory distress syndrome, relapsing Beheers colitis; asthma; rheumatoid arthritis; endotoxemia; endotoxic shock; Crohn's disease; fever, and flu-like symptoms; acute interstitial pneumonitis; septic and nonseptic shock; acute respiratory distress syndrome; thromboembolic conditions; bone resorption; arthritis; acute graft versus host disease; cerebral malaria; cachexia of tuberculosis or cancer; lung injury; and idiopathic fibrosis (page 47, line 1 to page 50, line 14; see also page 98, line 5 to page 110, line 3).

The test of definiteness is whether one skilled in the art would understand the scope of a claim when read in light of the specification. *Morton Int. Inc. v. Cardinal Chem Co.*, 5 F.3d 1464, 28 U.S.P.Q.2d 1190 (C.A.F.C. 1993); *Orthokinetics Inc. v. Safety Travel Chairs, Inc.* 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). While the Examiner cites to *In re Van Geuns*, 988 F.2d 1181, 26 U.S.P.Q.2d 1057 (Fed. Cir. 1993), to support his position ("[a]lthough the claims are read in light of the specification, limitations from the specification are not read into the claims"), the claims at issue in *In re Van Geuns* were rejected as being obvious in view of prior art, not as indefinite.

Therefore, the metes and bounds of the phrase "indication" would be readily recognizable and understood by the art worker in the absence of Applicant's specification or, alternatively, by the art worker in possession of Applicant's specification.

It is respectfully submitted that the pending claims are in conformance with the

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requirements of 35 U.S.C. § 112, second paragraph. Therefore, withdrawal of the § 112(2) rejection of claims 17 and 20 is respectfully requested.

The 35 U.S.C. § 112, first paragraph, rejections

The Examiner rejected claims 17, 20, 22, 34, 41-44, and 52-62 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Specifically, the Examiner alleges that 1) the phrase "a variant thereof, a derivative thereof" is not particularly described in the specification so that one or ordinary skill in the art would recognize that Applicant invented what is claimed; 2) there is no actual reduction to practice of the claimed invention; and 3) no disclosed correlation between structure and function, citing to *Univ. Calif. v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997).

The Examiner is respectfully requested to note that the claims are directed to the use of a peptide of a chemokine, a variant thereof, a derivative thereof, or a combination thereof, wherein the peptide comprises no more than 30 amino acid residues, wherein at least three contiguous residues of the peptide correspond to residues Trp-Val-Gln or Lys-Gln-Lys in the carboxyl-terminal half of the mature form of human MCP-1, and wherein the peptide inhibits the response induced by the corresponding native chemokine. Applicant discloses that a variant peptide of the invention has less than 100% homology to the corresponding amino acid sequence of a mature chemokine, i.e., a variant peptide has amino acid residues not present in the corresponding wild-type chemokine, e.g., amino acid substitution(s), internal deletion(s) or D-amino acid(s) (page 38). Chemokine peptides or peptide variants which are subjected to chemical modifications, such as esterification, amidation, reduction, protection and the like, are referred to as chemokine "derivatives" (page 38, line 17 through page 39, line 12).

Exemplary variant peptides of MCP-1 are Leu<sub>4</sub>Ser<sub>7</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1], which has amino acid substitutions at positions 4, 7 and 11 relative to the sequence of a 12 amino acid peptide of human MCP-1 designated peptide 3(1-12)[MCP-1], Ser<sub>7</sub>Glu<sub>8</sub>Glu<sub>9</sub>peptide3(1-12)[MCP-1], Leu<sub>4</sub>peptide3(1-12)[MCP-1], Ser<sub>7</sub>peptide 3(1-12)[MCP-1], Ile<sub>11</sub>peptide 3(1-

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12)[MCP-1], and Leu<sub>4</sub>Ile<sub>11</sub>peptide 3(1-12)[MCP-1] (see Table 3). The activities of these variants are shown in Table 4.

In Example 4, three derivatives of a variant of peptide 3[MCP-1] were prepared and tested. The derivatives were a cyclic-reverse D (CRD), a linear reverse-D (LRD), and a cyclic forward L (CFL), derivative of the variant Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1]. The MCP-1 inhibitory activity of these derivatives, as well as Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1], was determined. The results were LFL-Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1], 1-5 µM; LRD-Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1], 200-400 nM; CFL-Cys<sub>13</sub>Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1], 500-700 nM; and CRD-Cys<sub>13</sub>Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1], 50-100 nM, indicating that all of the derivatives had activity.

Clearly, Applicant's specification indicates that Applicant envisioned that peptides, corresponding to the carboxy-terminal half of a chemokine, as well as variant and derivatives thereof, are useful to inhibit or prevent indications associated with a chemokine-induced activity. Thus, contrary to the Examiner's allegations, Applicant has particularly described variants and derivatives of a chemokine peptide, provided an actual reduction to practice of the invention, and disclosed a correlation between the structure and function of the claimed chemokine peptides.

The facts in the present application are in contrast to those in *Univ. Calif. v. Eli Lilly & Co.*. In *Univ. Calif. v. Eli Lilly & Co.*, applicant's specification disclosed the cloning and sequencing of a rat insulin cDNA. The claims at issue were directed to isolated vertebrate and mammalian insulin cDNAs. The court ruled those claims invalid for lack of an adequate written description, reasoning that a description of rat insulin cDNA is not a description of vertebrate or mammalian insulin cDNA and that the description of a function of a gene, i.e., mammalian insulin cDNA, does not describe the structure of that gene.

Unlike *Univ. Calif. v. Eli Lilly & Co.*, Applicant's claims are directed to the use of chemokine peptides, variants and derivatives thereof which include residues corresponding to residues Trp-Val-Gln or Lys-Gln-Lys in the carboxyl-terminal half of the mature form of human MCP-1. Moreover, Applicant's specification describes the structure of numerous peptides falling within the scope of the invention.

Hence, Applicant's specification fully complies with the written description requirement of § 112(1).

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The Examiner rejected claims 17, 20, 22, 34, 41-44, 52-56, 59, and 61-62 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of preventing dermal inflammation or asthma using CRD-Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub>peptide 3(3-12)[MCP-1] allegedly does not reasonably provide enablement for 1) a method of preventing dermal inflammation or asthma using any peptide of a chemokine, a variant or a derivative thereof; or 2) a method of preventing an indication associated with chemokine induced activity using a peptide of a chemokine, a variant or a derivative thereof. These rejections are respectfully traversed.

First, the Examiner is requested to consider that the claims are directed to the use of a peptide of a chemokine, a variant, or a derivative thereof, wherein the peptide comprises no more than 30 amino acid residues, has at least three contiguous residues corresponding to residues Trip-Val-Gln or Lys-Gln-Lys in human MCP-1, and inhibits the response induced by a corresponding native chemokine. The Examiner is also requested to consider that Applicant's specification provides explicit and extensive guidance on how to identify peptides falling within the scope of the claims. For example, Table 1 illustrates an alignment of selected chemokines and indicates the general location of a peptide of the invention in human MCP-1, murine MCP-1, human MCP-2, human MCP-3, human MIP-1 $\alpha$ , human MCP-1 $\beta$ , RANTES, eotaxin, IL8 and human SDF-1b. Exemplary chemokines, from which the peptides of the invention may be obtained or derived, are listed at page 31, lines 4-24 of the specification, and include MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIG, MIP1 $\alpha$ , MIP1 $\beta$ , MIP2, RANTES, PF-4, I-309, HCC-1, eotaxin, C10, CCR-2, ENA-78, GRO $\alpha$ , GRO $\beta$ , GRO $\gamma$ , IL-8, IP-10, SDF1, SDF1 $\alpha$ , SDF1 $\beta$ , MIP3 $\alpha$ , TCA-3, CTAPIII, MARC/FYK,  $\beta$ -thromboglobulin, GCP-2, PBP, HC14, MDC, TECK, PARC, 6Ckine, fractaline, DC-CK1, LIX, TARC, LARC, Ck $\beta$ 8, CCF18/MRP-2, CCIII, CK $\alpha$ 2, H1305, Dvic-1, MGSA, Ck $\beta$ 4, DGWCC, TCA4, dendrokine, CC2/HCC1, CC3, and MIP1 $\tau$ , vMIP-I, vMIP-II and vMIP-III, NAP-2,  $\gamma$ IP, ENA78, lymphotactin, neurotactin and CCIII. Moreover, Applicant provides exemplary chemokine peptides in Figure 14.

It is further disclosed that a peptide of the invention may have 100% contiguous amino acid sequence homology or identity to the amino acid sequence of a native chemokine, or have less than 100% homology to the corresponding amino acid sequence of a nature chemokine, i.e., the peptide is a "variant" peptide. A variant peptide is thus disclosed as a peptide which has amino acid residues not present in the corresponding wild-type chemokine, e.g., amino acid

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substitution(s), internal deletion(s) or D-amino acid(s) (page 38). Chemokine peptides or peptide variants which are subjected to chemical modifications, such as esterification, amidation, reduction, protection and the like, are referred to as chemokine "derivatives." For example, a modification known to improve the stability and bioavailability of peptides *in vivo* is the cyclization of the peptide. Thus, a derivative of a peptide of the invention may include a CRD, LRD and CFL derivative of a peptide of the invention.

Moreover, the specification provides exemplary *in vitro* and *in vivo* assays to identify whether a chemokine peptide, a variant thereof, or a derivative thereof, inhibits or reduces a chemokine-induced activity (page 50, lines 16-25). These assays include *in vitro* assays (see page 50, line 27-page 52, line 28) which detect whether an agent inhibits the chemokine-induced chemotaxis of a variety of cell types (e.g., neutrophils, monocytes, eosinophils, mast cells, platelets or lymphocytes; page 52, lines 1-2), inhibits the release of enzymes from certain cells (such as N-acetyl- $\beta$ -D-glucosaminidase from monocytes or elastase from neutrophils; page 53, lines 2-13), changes the concentration of cytosolic free  $\text{Ca}^{2+}$  in various cell types (monocytes, eosinophils, neutrophils; page 53, line 15-page 54, line 18), inhibits binding to a chemokine receptor and/or displaces bound chemokine (page 54, line 20-page 55, line 27), and inhibits the co-mitogenic activity of a chemokine (page 56, lines 14-20).

Example 1 discloses the use of an *in vitro* chemotaxis assay, i.e., the inhibition of chemokine-induced THP-1 (a monocytic cell line) migration, to identify regions of human MCP-1 (hMCP1) falling within the scope of the invention. Example 4 describes that a CRD peptide variant of MCP-1 inhibited MCP-1-induced THP-1 migration. Table 2 shows the inhibition by a MCP-1 chemokine peptide of the MCP-1-, MIP1 $\alpha$ -, IL8- and SDF-1 $\alpha$ -induced migration of THP-1 cells and primary human monocytes. Table 4 shows ED<sub>50</sub> data for four chemokines (MCP-1, MIP1 $\alpha$ , IL8 and SDF-1 $\alpha$ ) and selected peptides which include variants of MCP-1 chemokine peptide, e.g., one variant peptide of human MCP-1 chemokine peptide (the variant is designated Leu<sub>4</sub>Ser<sub>7</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1]) has amino acid substitutions at positions 4, 7 and 11 relative to the sequence of a 12 amino acid peptide of human MCP-1 designated peptide 3(1-12)[MCP-1], and another variant (referred to as Ser<sub>7</sub>Glu<sub>8</sub>Glu<sub>9</sub>peptide3(1-12)[MCP-1]) has substitutions at positions 7, 8 and 9 relative to peptide 3(1-12)[MCP-1].

Table 4 also includes data from three chemokine peptides having three amino acid residues, one of which is a tripeptide from MIP-1 $\alpha$ . Some of the peptides described in Table 4 were found to be pan-chemokine inhibitors, while others showed selectivity for certain groups of chemokines, i.e., selectivity for CC or CXC chemokines. Example 6 discloses additional experiments for tripeptides of the invention. Thus, the tripeptide WVQ, a sequence found in the carboxy-terminal half of MCP-1, MCP-3, MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, eotaxin and IL8, inhibited all four chemokines tested, while tripeptide KQK, another sequence found in the carboxy-terminal half of MCP-1, was specific for MCP-1 (versus MIP-1 $\alpha$ , IL8 or SDF-1 $\alpha$ ). It is disclosed that the corresponding tripeptides for MIP-1 $\alpha$  (SEE), SDF-1 (KLK), and IL8 (KEN) were each specific for the cognate chemokine.

It is further disclosed that the efficacy of a peptide of the invention in an animal model may be assessed by clinical parameters specific for the particular model or by general parameters such as the extent of inflammation or cellular infiltration into affected tissues (page 66, lines 15-16). Animal models which may be employed to determine whether a peptide of the invention inhibits chemokine-induced activity *in vivo* are exemplified at pages 65-69 of the specification. For example, atherosclerosis is associated with chemokine-induced, e.g., MCP-1-induced, macrophage recruitment. Animal models of atherosclerosis include apoE knockout mice, mice which over express human apoB, and Watanabe heritable hyperlipidemic rabbits (page 66, lines 2-6). Animal models for autoimmune disease include collagen-induced arthritis in DBA/1 mice and myelin basic protein-induced experimental autoimmune encephalomyelitis. Animals models for osteoporosis include ovariectomized female rats, mice and monkeys, rats treated with heparin or glucocorticoids, and suspension-induced osteoporosis in rats. Thus, for atherosclerosis, the extent of lipid lesion formation in vessel walls may be determined in animals that have been administered a peptide of the invention relative to control animals (page 66, lines 24-29). For osteoporosis, bone density may be determined (page 100), as well as the presence bone matrix degradation products in plasma and urine (page 100), in animals that have been administered a peptide of the invention relative to control animals.

Methods to prepare therapeutic agents are described at pages 56-63 and 67-84 of Applicant's specification, and dosages, formulations and routes of administration of such agents are provided at pages 110-119 of Applicant's specification.

Thus, contrary to the Examiner's assertion ("[t]here is no guidance provided in the instant specification as to how one of ordinary skill in the art would generate a chemokine peptide variant or derivative other than those exemplified in the specification"), Applicant has provided explicit and extensive guidance as to how to identify peptides, including variants and derivatives thereof, which fall within the scope of the claims.

The Examiner also asserts that Applicant does not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of a chemokine peptide. The Examiner is requested to consider that CRD-Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub>peptide 3(3-12)[MCP-1] has amino acid substitutions relative to the amino acid sequence of the corresponding native chemokine, i.e., MCP-1. Moreover, Applicant's specification provides *in vivo* data generated using CRD-Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub>peptide 3(3-12)[MCP-1]. Further, as discussed hereinabove, variants including Leu<sub>4</sub>peptide3(1-12)[MCP-1], Ile<sub>11</sub>peptide3(1-12)[MCP-1], and Leu<sub>4</sub>Ile<sub>11</sub>peptide 3(1-12)[MCP-1] were all chemokine inhibitors (page 135, line 26 to page 137, line 7). In fact, the specification discloses that there were no substitutions which altered an amino acid residue in peptide3(1-12)[MCP-1] which markedly reduced the potency of the general chemokine inhibition observed (page 138, lines 9-13). With respect to derivatives of a chemokine peptide, as discussed above, all three tested derivatives had inhibitory activity.

To support the contention that amino acid substitutions can have "dramatic" effects on activity, the Examiner cites to Mikayama et al. (Proc. Natl. Acad. Sci. USA, 90, 10056 (1993)) and Voet et al. (Biochemistry, John Wiley & Sons, Inc., pp. 126-128 and 228-234 (1990)). Mikayama et al. relate that murine glycosylation inhibiting factor (mGIF) had one amino acid substitution relative to human macrophage inhibitory factor (hMIF) but that recombinant mGIF had a different activity than hMIF. Voet et al. review the molecular bases for hemoglobinopathies. Regardless, neither document evidences that amino acid substitutions in chemokine peptides have unpredictable effects on activity.

With respect to the "undue experimentation" alleged by the Examiner to be necessary to identify a chemokine peptide, a variant thereof, or a derivative thereof, falling within the scope of the claims other than those exemplified in the present specification, the fact that the outcome of such a synthesis/screening program is unpredictable is precisely why a screening program is

carried out. The Examiner simply cannot reasonably contend that a screening program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate bioactive molecules do not constitute undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to prepare and screen peptides of chemokines, substituted peptides of chemokines and derivatives thereof to locate additional peptides falling within the scope of the claims. See also, *Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a large number of peptides is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which the screening of large numbers of compounds has been standard practice for at least ten years (*Ex parte Forman*, 230 U.S.P.Q.2d 456 (Bd. App. 1986).

To support the assertion that it would require undue experimentation to carry out Applicant's invention, the Examiner cites to *Genentech v. Novo Nordisk*, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997) ("When there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required"). The claims at issue in *Genentech* were directed to a method of producing a cleavable human growth hormone (hGH) fusion protein. The specification described general applications for cleavable fusion expression, an enzyme (trypsin) that might be used for cleavage, and sites recognized by that enzyme. For its analysis, the court noted that in applicant's specification, "reasonable detail must be provided in order to enable members of the public to understand and

carry out the invention" (page 1005). The court found that the specification did not describe in any detail how to make hGH using a cleavable fusion protein expression system, reaction conditions under which cleavable fusion expression would work, or a specific cleavable fusion protein.

The *Genentech* court concluded that the claimed invention was the application of an unpredictable technology in the early stages of development, and so would require undue experimentation by the art worker to practice. Unlike *Genentech*, Applicant's specification provides more than adequate detail so that the art worker understands and can carry out the invention, i.e., the identification and preparation of peptides of a chemokine, variants thereof, and derivatives thereof, that inhibit the activity of at least one chemokine. Also in contrast to *Genentech*, exemplary peptides within the scope of the claims are described in the specification and have activity.

To further support the contention that it would require undue experimentation to carry out Applicant's invention, the Examiner asserts that pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons: a) the protein may be inactivated, i.e., by proteolytic degradation; b) the protein may not reach the target area because it is not able to cross the mucosa or may be adsorbed by fluids, cells, and tissues where it will have no effect; and c) other properties, such as adverse side effects, may make the protein unsuitable for treatment.

It is Applicant's position that the selection of suitable agents, dosage forms and routes of administration, e.g., those which have few or reduced adverse side effects and/or avoid inactivation, is well within the skill of the art worker (see, e.g., *In re Johnson*, 282 F.2d 370, 127 U.S.P.Q. 216 (C.C.P.A. 1960) (the selection of suitable dosages is within the skill of the art)).

Further, clinical data is not required to satisfy the enablement requirement for pharmaceuticals and methods of medical treatment. The standard is that the evidence provided by Applicant need not be conclusive that the disclosed agents are useful for the claimed method but merely convincing to one of skill in the art. *In re Brandstadter*, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973) and M.P.E.P. § 2164.05. Given Applicant's extensive disclosure discussed above, which includes *in vivo* data, one of ordinary skill in the art would be convinced that many chemokine

peptides, variants or derivatives thereof would be useful in methods to prevent or inhibit indications associated with chemokine induced activity.

If Applicant has provided a disclosure which enables the art worker to identify and use chemokine peptides falling within the scope of the invention, Applicant has complied with the enablement requirement of § 112(1).

It is respectfully submitted that the pending claims are in conformance with the requirements of 35 U.S.C. § 112, first paragraph. Therefore, withdrawal of the § 112(1) rejections of the claims is respectfully requested.

*Conclusion*

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at 612-373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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